REMARKS

Reconsideration is respectfully requested.

The Examiner notes that there was no claim 9 in the application as filed, and has re-numbered claims 10-26 as claims 9-25, and previously added claims 27-38 as claims 26-37.

Claims 26-27 and 29-37 have been amended. Claim 28 has been cancelled. Claim 38 has been added. Claims 26 and 35 have been amended to clarify the claimed invention. Claims 27-34 and 36-37 have been amended to correct the claim dependency resulting from the Examiner's objection to the claim numbering. Claims 26-27 and 29-38 are pending.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications. No new matter has been added.

Priority

The Examiner states that Applicants have not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration, or application data sheet allegedly fails to acknowledge the filing of any foreign application. The Examiner requests a new oath, declaration, or application data sheet in which the present application is identified by application number and filing date.

Applicants respectfully traverse this objection. The declaration correctly identifies the address of each inventor as required under 1.63(c)(1), and the priority claim to U.S. Provisional Application Nos. 60/134,406 filed May 17, 1999, 60/153,406, filed Sept. 10, 1999, and

60/159,783, filed Oct. 15, 1999. The application is a 371 of PCT/US00/13576, which is clearly identified in the Declaration.

Applicants have therefore met the requirements of 37 CFR 1.63(c). Applicants respectfully request that this ground for objection be withdrawn.

Objections to the Specification

The Examiner has objected to both the Abstract and the Specification.

A. Abstract

The Examiner objects to the Abstract. In particular, the Examiner states that the abstract uses legal phraseology such as "said," the abstract is over 150 words in length.

Applicants have filed a replacement Abstract that is in compliance with the rules for Abstracts. This ground for objection is therefore moot. Applicants respectfully request that it be withdrawn.

B. Specification

The Examiner has objected to the specification at page 10, line 20, and page 13, line 20. The Examiner states that the number 2 appears to be 3 as stated in the amended claims.

Applicants respectfully traverse this ground for objection. Applicants are not required to claim the exact range specified in the Specification, provided that the claimed subject matter is within the range disclosed. In this case, the range "between 3 and 50 amino acids" is within the range "between 2 and 50 amino acids" as stated in the Specification.

Applicants respectfully request that this ground for objection be withdrawn.

Claim Objections

Numbering of Claims

The Examiner notes that there was no claim 9 as originally filed, and has re-numbered claims 10-38 as claims 9-37.

Claim 35

The Examiner has objected to claim 35 as including an unwanted semi-colon between the word "an" and "amino." Applicants have amended claim 35 to correct this typographical error. This ground for objection is therefore moot. Applicants respectfully request that it be withdrawn.

Double Patenting

The Examiner has rejected claims 26-37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9 and 10 of U.S. Patent No. 6,329,336.

Applicants have filed a terminal disclaimer accompanying this response for claims 26-37 over U.S. Patent No. 6,329,336.

This ground for rejection is therefore moot. Applicants respectfully request that it be withdrawn.

Claim Rejections – 35 U.S.C. § 112 Enablement

The Examiner has rejected claim 26 as lacking enablement. The Examiner alleges that the specification, while enabling a method of synthesizing a modified therapeutic peptide and

coupling a succinimidyl-containing reactive group, does not reasonably provide enablement for synthesizing all therapeutic peptides with all reactive groups.

Applicants respectfully traverse, since the specification fully enables the amended claims.

A. The Legal Standard

Under 35 U.S.C. §112 ¶ 1, a patent specification containing a teaching of how to make and use the invention must be taken as enabling unless the PTO provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *ML T v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); In re *Jackson*, 217 U.S.P.Q. 804, 807 (PTO Pt. Bd. App. Int. 1982) (emphasis added). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited

to: 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

B. Meeting the Legal Standard

The Examiner has failed to meet the requisite burden showing a lack of enablement. Applicants provide extensive disclosure for the full breadth of the claims, including the disclosure of numerous therapeutic peptides, extensive guidance for synthesizing modified therapeutic peptides, and numerous specific examples of synthesizing modified therapeutic peptides having different numbers of cysteine residues. Contrary to the Examiner's position, the claimed methods do not require undue experimentation by those skilled in the art.

The nature of the claimed invention encompasses platform technology for synthesizing modified therapeutic peptides. The synthesis method is directed to synthesis of modified peptides by protecting or oxidizing cysteine groups, and requires very few, clearly described method steps, as shown at pages 74-85 of the Specification. Synthesizing modified therapeutic peptides by following the extensive guidance provided in the specification would hardly require the abilities of a doctoral scientist with several years experience, as alleged by the Examiner.

The breadth of the claimed invention is limited to modifying therapeutic peptides of specified length. The therapeutic peptides are limited to those having between 3 and 50 amino

acids. Further, the therapeutic peptides must have a carboxy-terminal amino acid and an amino terminal amino acid. The claims are directed to synthesis of modified therapeutic peptides having any number of cysteine residues.

Applicants provide substantial direction, guidance, and examples that show one skilled in the art how to perform the claimed methods. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). In the present case, Applicants provide extensive discussion of therapeutic peptides (Specification, page 11 line 27 through page 13, line 9). In particular, the specification discloses 1,617 distinct therapeutic peptides, along with discussion of the structure and function of their therapeutic qualities (Specification, page 13, line 16 through page 55, line 16). One of skill in the art has extensive guidance in the number and nature of therapeutic peptides.

The Specification also provides extensive and far-reaching guidance for synthesizing modified therapeutic peptides. The Specification discusses characteristics of modified therapeutic peptides from page 55, line 18 through page 69, line 18. The Specification also discusses methods of modifying therapeutic peptides with a reactive group from page 69, line 20 through page 74, line 7.

Further, Applicants provide an extensive discussion of how to synthesize modified therapeutic peptides having different numbers of cysteines. From page 74, line 9 through page 79, Applicants provide an extensive discussion, complete with chemical structures, of synthesizing modified therapeutic peptides that lack cysteine residues. From page 80, line 1,

though page 81, line 10, Applicants provide a similar discussion of how to synthesize modified therapeutic peptides containing only one cysteine. From page 81, line 11 through page 83, Applicants provide a detailed discussion and chemical structures for how to synthesize modified therapeutic peptides that contain two cysteines as a disulfide bridge. In addition, Applicants provide an extensive discussion of how to synthesize peptides containing multiple cysteines from pages 84-85. Applicants have thus provided extensive, chemically specific guidance to those skilled in the art on how to perform the claimed methods.

To augment the detailed directions for synthesizing modified therapeutic peptides, Applicants also provide 70 examples of synthesizing modified therapeutic peptides that have different numbers of cysteine residues. Examples 1-6 disclose methods of modifying the peptide chain to aid attachment of a reactive group. Examples 7-55 provide specific guidance for synthesizing numerous peptides having no cysteine residues. Examples 56-60 provide specific examples of preparing modified therapeutic peptides containing one free cysteine residue. Examples 61-64 provide specific examples of preparing modified therapeutic peptides containing two cysteine residues. Examples 65-70 provide specific examples of preparing modified peptides from peptides containing two or more cysteines.

Applicants have thus provided far-reaching, detailed guidance in how to perform the claimed methods. Applicants have disclosed over 1,617 therapeutic peptides, provided detailed chemical guidance in how to synthesize modified therapeutic peptides containing zero, one, two, or more cysteines, and have provided 70 examples of synthesizing modified therapeutic peptides. The methods do not require undue experimentation from one of ordinary skill in the art.

C. Specific Arguments Raised by the Examiner

Notwithstanding the guidance given by Applicants, the Examiner has made a number of arguments that are either unsupported or fail to take into account the extensive support present in the Specification.

First, although the Examiner admits that synthesis of polypeptides and covalently linking a reactive group is predictable, the Examiner argues that claims are not enabled because the biological function of a therapeutic peptide coupled to a blood component is unpredictable. To support this conclusion, the Examiner relies on the Knusli et al., *Brit. J. Heamatol.*, 82:654-663 (1992), which discusses a PEG-modified macrophage colony stimulating factor.

The Examiner's allegation is entirely without support, since Knusli et al. is directed to very different technology than that of the present invention. Specifically, Knusli et al. is directed to a PEG-modified peptide. The peptide disclosed by Knusli et al. is not coupled to a blood component to form a covalent bond, as required by the present claims, since PEG is merely a synthetic polymer, not a blood component. While blood components are functional in the cell, PEG is not functional in the cell.

Further, the Examiner appears to suggest that after following the claimed methods, the synthesized modified therapeutic peptides bonded to a blood component must have a specific level of activity. There is no such requirement in the claims. The present claims are simply directed to a method of synthesizing a modified therapeutic peptides with different numbers of cysteine residues.

Second, the Examiner alleges that the process of making and using the therapeutic peptide conjugate is not explained in detail for therapeutic peptides whose function is not completely understood, such as C-type natriuetic peptide. The Examiner further alleges that "the identification of a less therapeutic region and a more therapeutic region on a peptide [and] where the reactive group should be conjugated, whose function is not completely understood, would be difficult."

The amended claims are no longer directed to a "less thereapeutic region and a more therapeutic region." Further, performing the claimed methods does not require the function of a specific therapeutic peptide to be completely understood. The claims are directed to synthesizing a modified therapeutic peptide based on the number of cysteine residues present in the therapeutic peptide. The claimed methods do not include any limitation requiring a complete understanding of the function or mechanism of the therapeutic peptide. The methods thus may be performed regardless of how well the function of the therapeutic peptide is understood.

Third, the Examiner alleges that the working examples do not encompass all types of therapeutic peptides. The Examiner seems to insist that the specification should contain an example of synthesizing modified therapeutic peptide for every single peptide comprising between 3 and 50 amino acids.

Applicants need not provide a specific example of everything embraced by a broad claim. *In re Anderson* (CCPA 1973) 471 F.2d 1237, 176 USPQ 331. Indeed, enablement is not precluded by the need for some experimentation such as routine screening. *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). In the present application, Applicants have

provided 70 examples showing synthesis of modified therapeutic peptides. The therapeutic peptides in the Examples contain zero, one, two, or more cysteines. Applicants have provided more than a sufficient number of examples, particularly in view of the extensive detailed disclosure of how to synthesize the modified therapeutic peptide without undue experimentation.

Fourth, the Examiner alleges that there is a large quantity of experimentation necessary to determine the biological activity of all modified therapeutic peptide conjugates described in the Specification. The Examiner further alleges that the therapeutically less active region of peptides would not be known for conjugates of reactive groups.

As stated out previously and reiterated here, the amended claims do not require knowledge of the specific location of a more therapeutically active region or less therapeutically active region. The claims merely require that the therapeutic peptide is modified with a reacting group, and the reacting group is capable of reacting with amino groups, hydroxyl groups, or thiol groups on a blood component to form a covalent bond. One of ordinary skill in the art would thus not require knowledge of a more therapeutically active region or less therapeutically active region to perform the methods.

The Examiner fails to meet the requisite burden of showing that undue experimentation is required to perform the claimed invention. Applicants have provided extensive support enabling one of skill in the art to follow the claimed methods. Applicants respectfully request that the instant rejection be withdrawn.

Claim Rejections – 35 USC §102(e)

The Examiner has rejected claims 26(a), 27-32, and 35-37 under 35 U.S.C. § 102(e) as being anticipated by Ezrin et al., U.S. Patent No. 6,500,918.

This ground for rejection is improper, since U.S. Patent No. 6,500,918 is not prior art under 35 U.S.C. § 102(e). The correct 102(e) date of U.S. Patent No. 6,500,918 is December 16, 1999, not May 17, 1999, as alleged by the Examiner.

Under the AIPLA, international patent applications filed prior to November 29, 2000 are governed by former rule 35 U.S.C. §102(e), which states: "a person shall not be entitled to a patent unless...the invention was described in ... an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent." Therefore, for an international patent application filed prior to November 29, 2000, the 102(e) date of the resulting patent is the date the patent application enters the U.S. national phase (*i.e.* the date on which 371 (c)(1), (2), and (4) are met), and not the filing date of the international application.

In the present case, the cited reference U.S. Patent No. 6,500,918 is a divisional of U.S. Patent No. 6,437,092, which is the 371 U.S. national stage entry of PCT/US98/23704. PCT/US98/23704 was filed Nov. 6, 1998 (prior to November 29, 2000) and entered the U.S. national stage on December 16, 1999, its effective 102(e) date. The 102(e) date of U.S. Patent No. 6,500,918 therefore is the same Dec. 16, 1999 date.

Applicants claim priority to U.S. Provisional Application Nos. 60/134,406 filed May 17, 1999, 60/153,406 filed Sept. 9, 1999, and 60/159,783, filed Oct. 15, 1999. Each of these patent applications predate the 102(e) date of U.S. Patent No. 6,500,918.

Applicants further direct the Examiner to the "Office of Patent Legal Administration (OPLA) guide to USPTO 35 U.S.C. § 102(e) and 374 as amended H.R. 2215" a copy of which is provided with this response (in Appendix). Example P5A at page 29 is analogous to the present 102(e) rejection.

Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103(a)

The Examiner has rejected claims 26 and 27 under 35 U.S.C. § 103(a) as unpatentable over Ezrin et al. (U.S. Patent No. 6,550,918, effective filing date May 17, 1999). The rejection is improper on multiple grounds. First, Ezrin et al. is not a prior art reference under 35 U.S.C. § 102(e), as discussed above. Second, even if Ezrin et al. were a proper 102(e) reference, the rejection would still be improper under 35 U.S.C. § 103(c). Under § 103(c), "subject matter developed by another person which qualifies as prior art only under one or more of subsections (e), (f), and (g) ...shall not preclude patentability under [section 35 U.S.C. § 103] where the subject matter and the claimed invention were, at the time of invention was made, owned by the same person or subject to an obligation of assignment from the same person." Both Ezrin et al. and the present application were owned by, or under an obligation of assignment to assignee Conjuchem at the time the inventions were made. Therefore, the rejection under 35 U.S.C. § 103(a) is improper.

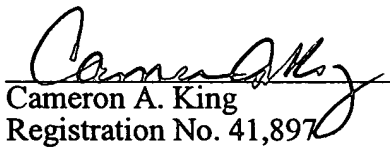
Applicants respectfully request that this ground for rejection be withdrawn.

Conclusion

In light of the above amendments and remarks, Applicants believe that this case is now in condition for allowance. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the Patent Office determines that an extension and/or other relief is required as a result of this statement, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to our **Deposit account no. 03-1952** referenced Docket No. **500862002100**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: December 19, 2003 By: 

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